" A prospective randomized double blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of postoperative deficits in patients undergoing elective neurosurgery for Supratentorial Intra Axial Mass Lesions"

A dissertation submitted to the Tamil Nadu Dr. M.G.R.Medical university in partial fulfilment of the requirement for the award of M.D.Branch II (anaesthesia) degree March 2012.

CERTIFICATE

This is to certify that this dissertation ***"A prospective randomized double blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of postoperative deficits in patients undergoing elective neurosurgery for Supratentorial Intra Axial Mass Lesions"*** work of research done by Dr. P. Aparanjit Paul, towards partial fulfilment of the requirements for the award of MD Anaesthesia degree.

Signature of the H.O.D,
Dr.Sarah Ninan,
Professor,
Dept of Anaesthesia,
CMC, Vellore.

CERTIFICATE

This is to certify that this dissertation ***"A prospective randomized double blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of postoperative deficits in patients undergoing elective neurosurgery for Supratentorial Intra Axial Mass Lesions"*** work of research done by Dr. P. Aparanjit Paul, towards partial fulfilment of the requirements for the award of MD Anaesthesia degree.

Dr.Grace Korula,
Professor,
Dept of Anaesthesia,
CMC, Vellore.

ACKNOWLEDGEMENTS

Firstly, I thank GOD for his grace and faithfulness.

My sincere thanks to Dr.Grace Korula, my giude,for her valuable guidance, patience and for encouraging me.

I am grateful to Dr.Aditya Vedantam,my co-investigator for his help and time spent in completing this project.

I express my sincere acknowledgements to Dr. Sarah Ninan Professor and Head of Department of Anaesthesia , Christian Medical College , Vellore for her help in this endeavour.

I am extremely grateful to my colleagues and my anaesthesia technicians without whose help this endeavour would not have been successfully completed. Their willingness to always help me in recruiting patients will always be remembered by me.

Thanks are due to the pateints who have been part of this study without which this study would not have been possible.

I thank my wife Dr.Vandana for her love, support and prayers.

Contents

Introduction

Supratentorial tumor resection often involves dissection close to eloquent areas of the brain. The ideal anaesthetic agent for neuroanaesthesia should preserve cerebral hemodynamics and provide rapid recovery to facilitate early detection of post-operative neurological deficits. Ideal anaesthetic agent should have adequate potency, low lipid solubility leading to quick induction and emergence. [1]Desflurane, a volatile inhalational anaesthetic agent, has a lower blood gas solubility compared to isoflurane (which is routinely used for neuroanaesthesia) and hence it causes quicker induction and emergence from anaesthesia.

Numerous factors determine the neurological condition of a patient following elective cranial surgery. A primary concern after any neurosurgical procedure is intracranial hematoma formation. Delayed neurological recovery or deterioration will need to be evaluated and appropriate intervention instituted without delay if a surgical cause is suspected. However, it has been noticed that a proportion of neurosurgical patients develop 'reversible' neurological deficits that improve within 12 hours after surgery, and cannot be attributed to structural damage during the surgery. Previous reports have suggested that anaesthetic agents may be responsible for reversible neurological deficits.

Thal et al[2] studied the effects of midazolam and fentanyl in unmasking neurological deficits in 54 patients (27 with supratentorial mass lesions and 27 with carotid disease) pre-operatively. They demonstrated a new or worsened motor deficit in 30% of the cases.[2] This study also postulated several possible mechanisms to explain this

phenomenon including, altered drug uptake, distribution and metabolism of drugs in abnormal brain and increased sensitivity to sedatives. They concluded that, transient neurological deficit post-operatively could also be the result of the same mechanisms. Our hypothesis is that the effect of the anaesthetic agent may be a significant contributor to the recovery of an early post-operative neurological deficit and desflurane, which causes a quicker recovery from anaesthesia, will show a more rapid improvement of the motor deficit. We aim to determine a time limit within which these factors play a role, and after which further investigations and/or interventions need to be planned.

Aims

To compare the effects of desflurane and isoflurane anaesthesia with regards to -

1. Time to emergence and recovery following elective neurosurgery for supratentorial mass lesions.

2. Time taken for improvement of early post-operative motor neurological deficits.

Objectives

To compare the effects of desflurane and isoflurane anaesthesia in relation to -

1. Recovery as determined by the time to eye opening, time to extubation, time to obeying commands and orientation, after elective neurosurgery for adult patients (18-70 years, ASA I-III) with supratentorial intraxial mass lesions.

2. Time to improvement of early post-operative motor deficits within the first 12 hours after surgery.

Literature review

The ideal anaesthetic agent for neuroanaesthesia should preserve cerebral hemodynamics and provide rapid recovery to facilitate early detection of post-operative neurological deficits.[1] It should also prevent increase in intracranial pressures (ICP), reduce cerebral metabolic rate of oxygen consumption. Desflurane, a volatile inhalational anaesthetic agent, has a lower blood gas solubility compared to isoflurane (which is routinely used for neuroanaesthesia) and hence it causes quicker induction and emergence from anaesthesia. However the use of desflurane in neurosurgery has been debated because of its increased vasodilatory property as compared to isoflurane and sevoflurane.

Solubility of a particular gas is expressed in terms of partition coefficient. Partition coefficient can be defined as the ratio of the concentration of anaesthetic gases in two phases at equilibrium. Equilibrium is defined as equal partial pressures in two phases. The partition[3] coefficients of desflurane, isoflurane, sevoflurane, and halothane are 0.42, 1.4, 0.65 and 2.4 respectively. The higher, the blood gas partition coefficient, the greater the anaesthetic solubility, the greater its uptake by the pulmonary circulation. As consequence of this high solubility alveolar partial pressure rises more slowly and induction is prolonged. Thus lower the blood gas solubility, faster will be the induction and emergence.

Desflurane is a non inflammable volatile anaesthetic. It has a vapour pressure of 681 at 20 degree Celsius and as such it boils at room temperature at high altitudes. This problem necessitates the development of a special desflurane vaporizer[3].

Vaporizer output depends on fresh gas flow, carrier gas composition, dial settings, and the drug used. Due to its unique physical characteristics, controlled vaporization of desflurane requires a novel approach to vaporizer design. Desflurane can be delivered using Tec 6 [5], Tec 6 plus and Aladin Cassette vaporisers. [4]

Effect of inhalational anaesthetics in General and Neurosurgery

Numerous studies have been done to compare the induction, recovery and emergence of patients receiving desflurane, halothane in neurosurgery and other specialties.

Leila Welborn et al [6] conducted a study on induction and recovery characteristics of desflurane and halothane anesthesia in pediatric outpatients. The anesthetic agents used were desflurane, halothane and nitrous oxide. Caudal block was given to all patients for post operative pain relief. These children underwent elective outpatient surgery such as hernia repair, circumcision and orchidopexy. This study showed that, airway complications (coughing, breath holding, and laryngospasm) were significantly higher among the children induced with desflurane than among either of the halothane induction groups. Premedication had no effect on reducing the number of airway complications. Emergence and recovery times (mean ± SD) were significantly shorter among both desflurane maintenance groups (3.6 ± 1.7 and 11 ± 8 min) than among the group maintained on halothane (7.9 ± 3.5 and 29.9 ± 10.6 min respectively).

In the study performed by S.R. Wrigley et al[7] , on Induction and Recovery characteristics of desflurane, it was found that the low blood/gas partition coefficient of desflurane would be useful agent for ambulatory surgeries and that a rapid induction and recovery would be possible.

Comparison of Desflurane, Isoflurane and Propofol:

Propofol (2, 6-diisopropylphenol) is an I.V induction agent with a high lipid solubility resulting in a very rapid onset of action. It also has a very short distribution of life (2-8 min) resulting in rapid awakening. Propofol decreases cerebral blood flow and intracranial pressure. It also has got anti- emetic and anti-pruritic properties.

S.R. Wrigley et al compared desflurane with propofol for use in day care patients. In this study, the inhalational anesthetic agents used were desflurane and nitrous oxide. Intravenous agents used were propofol and fentanyl. [7]This study shows that desflurane offers a short induction and recovery period and is suitable agent for general anaesthesia for outpatient procedures.

Visser, Klazina M.D et al[8], performed a randomized controlled trial of Total Intravenous Anesthesia (TIVA) with propofol versus inhalation anesthesia with isoflurane-nitrous oxide, to assess the incidence of postoperative nausea and vomiting. The inhalationa anaesthetic agents used in this study were isoflurane and nitrous oxide and propofol was used as TIVA. This study was conducted in non selected surgical patients. This study showed that TIVA reduced the absolute risk of postoperative nausea and vomiting up to 72 h by 15% among inpatients (from 61% to 46%, $P < 0.001$) and by 18% among outpatients (from 46% to 28%, $P < 0.001$). This effect was most pronounced in the early postoperative period. Median duration of stay in the post anesthesia care unit was 135 min after isoflurane versus 115 min after TIVA for inpatients ($P < 0.001$) and 160 min after isoflurane versus 150 min after TIVA for outpatients ($P = 0.039$). Duration of hospitalization was equal in both arms. Propofol TIVA results in a clinically relevant reduction of postoperative nausea and vomiting compared with isoflurane-nitrous oxide anesthesia (number needed to treat = 6). Both

anesthetic techniques were otherwise similar. Anesthesia costs were more than three times greater for propofol TIVA, without economic gains from shorter stay in the post anesthesia care unit.

CPP, ICP, MAP:

The anaesthetic care of patients who undergo neurosurgery requires a basic understanding of physiology of central nervous system.

The Cranial vault is rigid structure with a fixed total volume, consisting of brain (80%), blood (12%) and CSF (8%). Any increase in one component must be offset by an equivalent decrease in another to prevent a rise in ICP.

Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). CPP is normally 80- 100 mm of hg. ICP is normally less than 10mm of hg.

Effect of anaesthetic agents on cerebral haemodynamics

Kaye A, et al [9] compared the effects of desflurane and isoflurane on cerebral perfusion pressure (CPP), lumbar cerebrospinal fluid pressure (LCSFP), and mean arterial blood pressure (MAP) in patients anaesthetized with desflurane or isoflurane undergoing craniotomy for supratentorial mass lesions. Additionally, emergence from anaesthesia was examined to determine if neurologic function could be assessed earlier after isoflurane or desflurane anaesthesia.

They found that CPP was not significantly different between the two groups. The patient's time to respond to commands, was 50% shorter in the desflurane group (30 +/- 36 min) (mean +/- SD) when compared with the isoflurane group (72 +/- 126

min); however, this was not significant (P = 0.17). In patients undergoing craniotomy for supratentorial mass lesions, desflurane and isoflurane have similar effects on CPP and MAP. Additionally, desflurane in the setting of hyperventilation does not cause significant changes in LCSFP. This is the largest study to date comparing the effects of desflurane and isoflurane on patients undergoing craniotomy for supratentorial mass lesion with evidence of midline shift or edema. Neither desflurane nor isoflurane significantly altered lumbar cerebrospinal fluid pressure when moderate hypocapnia was maintained.

Fraga M et al [10] performed a study on effects of isoflurane and desflurane on intracranial pressure, cerebral perfusion pressure, and cerebral arteriovenous oxygen content difference in normocapnic patients with supratentorial brain tumors.

The purpose of this study was to determine the variations on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) as well as on cerebral arteriovenous oxygen content difference in normocapnic patients scheduled to undergo removal of supratentorial brain tumours with no evidence of mass effect during anaesthesia with isoflurane or desflurane.

Intravenous agents used in this study were fentanyl, thiopentone and vecuronium. Inhalational agents used were desflurane and isoflurane. This study showed that there were no significant differences between groups in heart rate, mean arterial pressure, ICP, and CPP. ICP measurements throughout the study did not change within each group compared to baseline values. In conclusion there are no variations on ICP in normocapnic patients undergoing removal of supratentorial brain tumours without midline shift, as they were anesthetized with isoflurane or desflurane. CPP and cerebral $AVDo_2$ decreased with both agents.

In a study done by Young, William L. M.D etal[11] , CBF values were compared between desflurane and isoflurane at two doses. In addition, CBF reactivity to CO2 and the effect of prolonged exposure were compared between the two agents. 133Xenon was used to measure Cerebral Blood Flow. This study was done in patients undergoing craniotomy for mass lesions. This study showed that there was no demonstrable decrease in CBF with prolonged exposure to either agent. Desflurane and isoflurane were similar in terms of absolute CBF, the response to increasing doses, and the preservation of CO2 reactivity.

Smiley et al[12] conducted a randomized controlled study in 28 patients to compare time of emergence from anesthesia in patients undergoing elective surgery under desflurane anesthesia to that of patients under isoflurane anesthesia. The anesthetics used in this study were Thiopentone, Nitrous Oxide and Desflurane. The times from discontinuation of anesthetic gases until patients opened their eyes and squeezed the investigator's hand in response to a command were averaged and recorded as "emergence time." This study confirmed that, emergence time was significantly less with desflurane than with isoflurane given at the same MAC.

Azad et al[13] made a study to compare desflurane with Isoflurane in several anesthetic situations such as intubation conditions, hemodynamic response to intubation, maintenance haemodynamics, and speed of recovery from desflurane and isoflurane anaesthesia. In addition, interactions with a muscle relaxant at low and high concentrations of the anaesthetics were compared. This study was done in 32 patients undergoing lengthy orthopedic procedures. The anesthetics used in the study were Thiopentone, Desflurane, Isoflurane and Pancuronium. This study showed that, desflurane is similar to isoflurane in providing anesthesia for intubation and

maintenance. Desflurane tends to increase HR and occasionally causes a hyper dynamic response during rapid deepening of anesthesia. It is very similar to isoflurane in its interaction with pancuronium.

K. Gerlach et al [14] conducted a study on effects of a propofol/ sufentanyl versus a remifentanyl/ propofol regimen on the primary end-point tracheal extubation time. This was a randomized controlled trial using Total intravenous anaesthesia (TIVA). Remifentanyl has unique pharmacokinetics that might allow faster recovery after neurosurgery. It is used for fast-tracking patients after coronary by-pass surgery. Intravenous drugs used in this study were sufentanyl, propofol and remifentanyl. This study was conducted in 36 patients undergoing craniotomy for supratentorial mass lesions. This study showed that patients in the remifentanyl/propofol group were extubated earlier (mean times 6.4 (±SD 4.7) versus 14.3 (±9.2) min; P = 0.003). The two groups were similar with respect to postoperative nausea and vomiting, and patient-reported pain scores. Fifty per cent of the remifentanyl/propofol patients and 88% of the sufentanil / propofol patients required no analgesics within 1 h after operation (P= 0.03). The remifentanyl/propofol regimen provided quicker recovery. The two regimens were similar in terms of postoperative nausea and vomiting and patient-reported pain scores, but patients in the remifentanyl/propofol group required more analgesics within 1 h postoperatively.

Anaesthetic agents in Non- neurosurgical Surgeries.

Studies have been done in non neurosurgical patients to compare emergence and recovery from various inhalation anaesthetics. Ebert, Thomas et al [15]performed a study comparing sevoflurane with isoflurane, propofol anaesthesia. The study included recovery endpoints from controlled, randomized, prospective studies that

compared sevoflurane to isoflurane or propofol when extubation was planned immediately after completion of elective surgery in adult patients.

Sevoflurane was compared to isoflurane in eight studies (N = 2,008) and to propofol in three studies (N = 436). Analysis of variance was applied using least squares method means values to calculate the pooled mean difference in recovery endpoints between primary anaesthetics. The effects of patient age and case duration also were determined.

This study showed that sevoflurane resulted in statistically significant shorter times to emergence (‑ 3.3 min), response to command (‑ 3.1 min), orientation (‑ 4.0 min) and first analgesic (‑ 8.9 min) but not time to eligibility for discharge (‑ 1.7 min) compared to isoflurane (mean difference). Times to recovery endpoints increased with increasing case duration with isoflurane but not with sevoflurane (patients receiving isoflurane took 4 ‑ 5 min more to emerge and respond to commands and 8.6 min more to achieve orientation during cases longer than 3 hr in duration than those receiving sevoflurane). Patients older than 65 yr had longer times to orientation, but within any age group, orientation was always faster after sevoflurane. There were no differences in recovery times between sevoflurane and propofol. Recovery from sevoflurane was 3 ‑ 4 min faster than with isoflurane in all age groups, and the difference was magnified in longer duration surgical cases (> 3 hr).

Andrew Agoliati, BA et al[16] performed meta-analysis of average and variability of time to extubation comparing isoflurane with desflurane or isoflurane with sevoflurane. Medline search through December 2009 was used to identify studies with humans randomly assigned to isoflurane or desflurane groups without other

differences (e.g., induction drugs) between groups, and (2) mean and SD reported for extubation time and/or time to follow commands. The search was repeated for random assignment to isoflurane or sevoflurane groups. They considered extubation times >15 minutes (representing 15% of cases in the anaesthesia information management system data) to be prolonged. This study showed that desflurane reduced the mean extubation time by 34% and reduced the variability in extubation time by 36% relative to isoflurane. These reductions reduced the incidence of prolonged extubation times by 95% and 97%, respectively. Sevoflurane reduced the mean extubation time by 13% and reduced the SD by 8.7% relative to isoflurane. These reductions reduced the incidence of prolonged extubation times by 51% and 35%, respectively.

Brita Larsen et al [17] performed a study on recovery of cognitive function after remifentanyl-propofol anaesthesia. They compared the recovery characteristics of remifentanyl, desflurane and sevoflurane when used for anaesthesia in elective operative procedures.

In this study, the inhalational agents used were desflurane, sevoflurane and nitrous oxide. The intravenous agents used were fentanyl, remifentanyl and propofol. In this study, 60 patients aged 18–65 yr, were randomly assigned to receive remifentanyl-propofol, desflurane-N_2O, or sevoflurane-N_2O anesthesia. Early recovery times and a modified Aldrete Recovery Score > 9 were recorded. Trieger Dot Test and Digit Substitution Test (DSST) were performed the day before surgery and in the postanaesthesia care unit to evaluate intermediate recovery. This study showed that the remifentanyl-propofol group had a significantly faster emergence than desflurane or sevoflurane, with no difference between both inhaled anaesthetics. Thirty minutes after anaesthesia administration, patients in the remifentanyl-propofol and in the

desflurane groups gave significantly more correct responses in the DSST compared with sevoflurane (remifentanyl 87%, desflurane 83%, sevoflurane 56%), the impairment in the sevoflurane patients corresponding to the effects of a blood alcohol level of approximately 0.1% and, thus, being of clinical importance. Ninety minutes after anesthesia administration, no significant difference could be demonstrated among the groups in the DSST scores.

Emergence and return of cognitive function was significantly faster after remifentanyl-propofol compared with desflurane and sevoflurane up to 60 min after anaesthesia administration.

W. Wilhelm et al[18] made a study on 44 patients undergoing carotid endarterectomy, to compare recovery after general anaesthesia with desflurane supplemented with either remifentanyl or fentanyl. The result showed that emergence from remifentanyl-desflurane anaesthesia was significantly quicker than that from fentanyl-desflurane.

S. Gergin et al [19] made a study to compare the haemodynamic, emergence and recovery characteristics of sevoflurane with those of desflurane in nitrous oxide anaesthesia. This randomized control study took place in 40 patients undergoing Cholecystectomy. The anaesthetic agents used in this study were midazolam, fentanyl, thiopentone, vecuronium, sevoflurane, desflurane and nitrous oxide. This study showed that desflurane, like sevoflurane, maintains haemodynamic stability during intraoperative period. Although the duration of anaesthesia was longer, early recovery profile was rapid in desflurane group. The difference between late recoveries was comparable between groups.

M.H. Nathanson et al[20] made a study to compare recovery characteristics of desflurane and sevoflurane for maintenance of ambulatory anaesthesia. In this study 42 patients undergoing laparoscopic sterilization were enrolled. The anaesthetic agents used in this study were propofol, fentanyl, vecuronium, desflurane, sevoflurane and nitrous oxide. This study showed that, although sevoflurane was associated with a slower emergence from anesthesia than desflurane after laparoscopic surgery, recovery of cognitive function and discharge times were similar in the two anesthetic groups.

Recovery Score

It is very important to monitor recovery from anaesthesia. In 1970, Aldrette developed a post anaesthesia scoring system[21] to monitor recovery from anaesthesia .The original Aldrette Score assigned a number of 0, 1 or 2 to five variables i.e., Activity, Respiration, Circulation, Consciousness and Colour. A score of nine out of ten was considered adequate for discharge from PACU. (Post Anaesthesia Care Unit).In 1995, Pulse Oximetry replaced the visual assessment of oxygenation and additional assessments were added to accommodate patients undergoing ambulatory surgery.

As the number and complexity of outpatient surgeries increased, the discharge criteria have been amended by various authors.

Post Anaesthesia discharge scoring system (PADSS) is one such a criterion. It is based on five criteria i.e. vital signs, ambulation and mental status, pain and nausea, surgical bleeding and fluid intake/output. Patients achieving a score of nine are acceptable for discharge.

Respiration

2= Able to take deep breath and cough

1= Dyspnoea /shallow breathing

0= Apnoea

O_2 Saturation

2= Maintains >92% on room air

1= Needs O2 inhalation to maintain O2 saturation >90%

0= Saturation < 90% even with supplemental oxygen

Consciousness

2= fully awake

1= Arousal on calling

0= Not responding

Circulation

2= BP$\pm$ 20mm HG pre op

1= BP$\pm$ 20- 50 mm HG pre op

0= BP$\pm$ 50mm HG pre op

Activity

2= Able to move 4 extremities

1= Able to move 2 extremities

0= Able to move 0 extremities

The total score is 10. Patients scoring $\geq$ 8 (and/or are returned to similar pre op status) are considered fit for transition to Phase II recovery

J Dupont et al[22]made a study on maintenance and recovery profiles after general anaesthesia with sevoflurane, desflurane and isoflurane in 100 patients undergoing pulmonary surgery. In this study, End-tidal concentrations of anaesthetic required to maintain mean arterial pressure and heart rate within 20% of baseline values were 1.4 +/- 0.6% for sevoflurane, 3.4 +/- 0.9% for desflurane and 0.7 +/- 0.3% for isoflurane. This study showed that the three anaesthetics had comparable haemodynamic effects and arterial oxygenation during one-lung ventilation. Emergence was twice as fast

with desflurane as with sevoflurane or isoflurane (mean times to extubation: 8.9 (SD 5.0) min, 18.0 (17.0) min and 16.2 (11.0) min for desflurane, sevoflurane and isoflurane, respectively).

Early recovery (Aldrete score, cognitive and psychomotor functions) was also more rapid after desflurane. In pulmonary surgery, desflurane, but not sevoflurane, allowed more rapid emergence and earlier recovery than isoflurane.

Paul .F. White et al[23] made a study to know the effect on early versus late recovery and per operative coughing by using desflurane or sevoflurane for maintenance of anesthesia in the ambulatory setting. This study was done in 130 patients undergoing superficial surgical procedures .The anesthetic agents used in this study were propofol, sevoflurane, desflurane, air and ketorolac. This study showed that use of desflurane for maintenance of anaesthesia was associated with a faster emergence and a higher incidence of coughing. Despite the faster initial recovery with desflurane, no significant differences were found between the two volatile anesthetics in the later recovery period. Both desflurane and sevoflurane should be available for ambulatory anesthesia.

Ghour et al[24] made a study to compare recovery profile after desflurane-nitrous oxide and isoflurane-nitrous oxide in outpatients. This study was done in 38 outpatients undergoing elective surgical procedures. The anesthetic agents used in this study were desflurane, isoflurane, nitrous oxide, fentanyl, thiopentone and succinyl choline. This study showed that postoperatively, patients who received desflurane exhibited less impairment of cognitive function (as measured using the DSST) than did those who received isoflurane. Furthermore, visual analog scores indicated that patients

receiving desflurane experienced significantly less discomfort (pain), drowsiness, fatigue, clumsiness, and confusion in the early postoperative period.

Beaussier[25] made a study to compare the effects of desflurane and isoflurane on recovery after long lasting anaesthesia. The aim of the study was to compare anaesthesia recovery after desflurane and isoflurane, administered for more than three hours. This study showed that after long duration anaesthesia lasting up to three hours, desflurane allowed recovery and extubation in approximately half the time required by isoflurane. Less variability in results suggests better predictability of recovery with desflurane.

G. R. Nordmann et al [26] studied emergence and recovery in children after desflurane and isoflurane anaesthesia. In this study, the inhalational agents used were desflurane and isoflurane. Fifty-four infants and children assigned in groups according to age and expected length of operation were prospectively randomized to receive either isoflurane (I) or desflurane (D) for anaesthesia. This study showed that for patients <4 yr of age, the median (95% CI) times in minutes to first movement [5.27(D), 9.22 (I)], eye opening [9.42(D), 13.3(I)] and extubation [7.18 (D), 12.5 (I)] were significantly shorter ($P<0.05$) for desflurane. In the group >4 yr of age, the median (95% CI) times in minutes to first movement [4.42 (D), 11.6 (I)], eye opening [8.55(D), 18.0(I)] and extubation [7.08 (D), 16.7 (I)] were significantly shorter ($P<0.001$) for desflurane. Times to leave recovery were not significantly different for the group <4 yr of age, but were significantly shorter for desflurane in the group >4 yr of age ($P<0.01$). The isoflurane, but not desflurane, had a time-dependent effect on arousal. There were no significant differences in incidence of airway irritation or emergence delirium between the two agents. It can be concluded that, the rate of recovery was faster in

children after exposure to desflurane than those patients receiving isoflurane. Recovery from desflurane, but not isoflurane, was relatively unaffected by the duration of anaesthesia.

Recovery after neurosurgery:

Desflurane in neurosurgery is beneficial because it facilitates postoperative early neurologic evaluation. However, its use has been debated because of its capacity to promote cerebral vasodilatation and sevoflurane has been extensively used in neurosurgical patients. Giuseppina Magni et al[27] in a prospective clinical trial compared early postoperative recovery and cognitive function in patients undergoing craniotomy for supratentorial expanding lesions and receiving sevoflurane or desflurane anaesthesia. In this study, the inhalational agents used were desflurane and sevoflurane. Emergence time was measured as the time from drug discontinuation to the time at which patients opened their eyes; tracheal extubation time was measured as the time from anaesthetic discontinuation and tracheal extubation. Recovery time was measured as the time elapsing from discontinuation of anaesthetic and the time when patients were able to recall their name and date of birth. Cognitive behaviour was evaluated with the Short Orientation Memory Concentration Test. In the post anaesthesia care unit, a blinded observer monitored the patients for 3 h; the incidence of hemodynamic events, pain, nausea, and shivering requiring rescue medication was recorded.

This study shows that the Short Orientation Memory Concentration Test score differed between the two groups only at the earliest assessment (15 min after extubation). No difference between the two groups was found in pain, shivering, nausea, vomiting, and incidence of postoperative hemodynamic events. It can be

concluded that patients who received desflurane had a shorter extubation and recovery time but similar intraoperative and postoperative incidence of complications compared with those who received sevoflurane.

Numerous factors, determine the neurological condition of a patient following elective cranial surgery. A primary concern after any neurosurgical procedure is intracranial hematoma formation. Delayed neurological recovery or deterioration will need to be evaluated and appropriate intervention instituted without delay if a surgical cause is suspected.

Early emergence from anaesthesia is essential following neurosurgery for neurological evaluation. Zelcer and Wells found a 9% incidence [28]of unresponsiveness at the end of 15 min after general anaesthesia among 443 mixed surgical patients. Arousal beyond 15 min and 30 min is termed as delayed emergence. Residual anaesthesia may either give the false impression of a neurological deficit or prevent the early diagnosis of a developing intracranial lesion like hematoma, herniation and cerebral infarction. A patient with altered sensorium is also at greater risk for airway obstruction, hypoxemia, hypercarbia and aspiration. The most common cause for delayed awakening following anaesthesia is medications and anaesthetic agents used in the per operative period there may be an overdose (absolute or relative in susceptible patients) of medications. Emergences from anaesthetic agents depend on the tissue uptake of the drug, average concentration used and the duration of exposure. Certain underlying metabolic disorders such as hypoglycemia, severe hyperglycemia, electrolyte imbalance (especially hyponatraemia), hypoxia, hypercapnia, central anticholinergic syndrome, chronic hypertension, liver disease, hypoalbuminemia, uremia and severe hypothyroidism may also be responsible for

delayed recovery after anaesthesia. Preoperative medications such as opioids and sedatives and hypothermia can further interfere with postoperative recovery.

Delayed Awakening

Arousal beyond 15 min and 30 minutes is termed as delayed emergence.[29]It is important to avoid conditions that lead to delayed awakening in patients. Liver disease reduces hepatic drug metabolism and biliary excretion resulting in prolonged drug action. Reduced serum, albumin levels increase free drug availability and prolong action. Kidney disease decreases renal excretion of many drugs and prolongs that action. Severe Hypothyroidism is associated with impaired drug metabolism and can also cause delayed awakening. Hypothermia decreases Minimum alveolar concentration, antagonizes muscle relaxation reversal and limits drug metabolism.

Intraoperative hypothermia is common and persists for several hours after surgery. Hypothermia may prolong immediate recovery by augmenting anesthetic potency, delaying drug metabolism, producing hemodynamic instability, or depressing cognitive function.

Lenhardt, Rainer MD et al [30] performed a study to assess effect of temperature on post anaesthetic recovery. This study was done in 150 patients undergoing major abdominal surgery. The anaesthetic agents used in this study were isoflurane, nitrous oxide and fentanyl. They were randomly assigned to routine thermal management (hypothermia) or extra warming (normothermia). Postoperative surgical pain was treated with patient controlled analgesia. Fitness for discharge from the post anaesthesia care unit was evaluated at 20min intervals by investigators blinded to group assignment and postoperative core temperatures. This study shows that

hypothermic patients required [nearly =] 40 min longer (94 +/ - 65 vs. 53 +/ - 36 min) to reach fitness for discharge, even when return to normothermia was not a criterion (P < 0.001). Duration of recovery in the two groups differed by [nearly =] 90 min when a core temperature > 36 [degree sign] Celsius was also required (P < 0.001).It was concluded that maintaining core normothermia decreases the duration of post anesthetic recovery.

Elderly patients have medical and psychological problems affecting all major organ systems.[31] These problems may alter the pharmacokinetics and/or pharmacodynamics of medications, or expose previous neurological deficits simply due to sedation. Delayed arousal, therefore, may arise from structural problems that are pre-existent or new, or metabolic or functional disorders such as convulsive or non-convulsive seizures.

Obesity

Obesity can be defined as BMI (body mass index >= 30) and extremely obesity as >=40. Due to the presence of large fat stores in obese people elimination of anaesthetics may be prolonged.

L. La Colla et al [32] performed a study to compare desflurane with sevoflurane kinetics and dynamics in morbidly obese patients undergoing elective bilio-intestinal bypass surgery. Twenty-eight unpremedicated obese patients were randomly allocated to receive either sevoflurane (n = 14) or desflurane (n = 14) as the main anaesthetic agent. After induction of anaesthesia, either sevoflurane 2% or desflurane 6% was administered for 30 min via a non-rebreathing circuit. The kinetics of sevoflurane and

desflurane were determined by measuring and recording end-tidal samples during this time. The bispectral index was used to indicate the level of hypnosis.

This study showed that the F_A/F_I ratio was significantly higher in the desflurane group from the 15th to the 30th min. Desflurane provided faster wash-in and wash-out than sevoflurane in morbidly obese patients, and recovery was much faster after desflurane administration when no premedication had been used.

Emergence from general anaesthesia has been a process characterized by large individual variability. Delayed emergence from anaesthesia remains a major cause of concern both for anesthesiologist and surgeon. The principal factor, for delayed awakening from anaesthesia is assumed to be the medications and anaesthetic agents used in the perioperative period. However, sometimes certain non-anaesthetic events may lead to delayed awakening or even non-awakening from general anaesthesia.

G. R. Nordmann et al [26] performed a study on Effect of anaesthetic duration on Emergence and recovery in children after desflurane and isoflurane anaesthesia.They hypothesized that, increasing duration of inhalation anaesthesia is associated with slower emergence and recovery in children, and that this effect would be less marked with desflurane in comparison with isoflurane.

Anil Gupta et al[33] made a systematic review to focus on post operative recovery and complications using propofol, sevoflurane, desflurane and isoflurane. They made a review from 58 articles. The review showed no differences between Propofol and Isoflurane in early recovery. However, early recovery was faster with desflurane compared to propofol and with sevoflurane compared to Isoflurane. A minor difference was found in home readiness between sevoflurane and Isoflurane, but not with any other anaesthetics. They concluded that the differences in early recovery

times among the different anaesthetics were small and in favour of inhaled anaesthetics. The incidence of side effects specifically post operative nausea and vomiting was less frequent with propofol.

Blood brain Barrier. (BBB)

Maintaining the integrity of blood brain barrier is essential for the homeostasis of brain. Even with minimum destruction of BBB, circulating neurotoxins, ions and hormones could enter the brain and interfere with the internal milieu, resulting in potential damage to neurons. Anaesthesia can decrease the permeability of BBB.

Oak Zichi [34]et al made a study in rats to study the effects of morphine on BBB disruption caused by intracarotid injection of hyperosmolar mannitol in rats .The study suggested that morphine may be effective in reducing the BBB caused by hyperosmolar mannitol without significant effects on systemic blood pressure.

In the majority of body's capillary beds[35] there are fenestrations approximately 65Amstrogs in diameters between endothelial cells. In the brain, with the exception of choroid plexus, the pituitary and Area Postrema, tight junctions reduce this space to approximately 8 Amstrongs. As a result, large molecules and most ions are prevented from entering the brains interstitium. There is little evidence that anaesthetics alter the function of this blood brain barrier. Acute hypertension can breach the barrier and certain anaesthetics facilitate this phenomenon.

Inadequate perfusion and supply of substrate induces energy failure. This translates into real effects on the integrity and function of BBB which is an energy dependant physiologic construct. Ischemia and rapid reperfusion are associated with the generation of metalloproteinase's that directly attack the proteins, sealing the connection between the endothelial processes that make up the BBB.

This creates a loss of integrity and increased porosity of the BBB pathologically affecting the permeability and reflection coefficients. This acute BBB destruction may allow shift into the parenchyma and result in brain swelling, the extent of which depends on the leakiness of the BBB as well as the size and concentration of osmotic ally active molecules on either side of the barrier.

Hence, fluid therapy needs to be carefully considered under circumstances of cerebral ischemia and inflammation. W.C.Cosolo[36] conducted a study to determine the optimum conditions for blood-brain barrier disruption without producing neurological sequelae. In this study, adult Sprague-Dawley rats were infused with mannitol via the internal carotid artery at rates varying from 0.25 to 0.5 ml/kg/s. Methotrexate and Evans blue were used as markers of blood-brain barrier disruption. The optimum rate of mannitol that produced blood-brain barrier disruption without neurological sequelae was 0.25 ml/s/kg for 20 s. The duration of blood-brain barrier opening was maximal for approximately 5 min and then rapidly reversed. Methotrexate levels on the mannitol-infused side were four to five times that of the noninfused hemisphere. This model should prove useful in the investigation of the treatment of intracerebral tumors with blood-brain barrier disruption. This study shows that maximal intracerebral methotrexate levels were obtained when methotrexate was infused before or within 5 min of the mannitol infusion.

Foster and et al[35]observed that the extravasations of the Evans Blue into Rabbit brain was greater when acute hypertension occurred during Anaesthesia with Halothane than with Thiopentone. It is likely that the effect is a nonspecific result of cerebral vasodilatation, rather than specific effect of halothane. These results were obtained in a setting of extreme abrupt hypertension in animals with an initially normal BBB.

There have been case reports in the past reporting neurological deficits after use of anaesthetic drugs mainly benzodiazepines.

Richard A Miller MD et al [37]have reported a patient with cervical spondylosis developing exacerbation of spinal neurological deficit during sedation with Diazepam and droperidol. This patient became substantially weaker after receiving Diazepam and droperidol prior to intubation despite normal blood gas tension, blood pressure and neck stabilization. They postulated that under some conditions sedative-hypnotics and tranquillizers can exacerbate or unmask existing spinal cord dysfunction.

A transient ischemic attack (TIA) in the brain is classically considered a syndrome lasting <24 hours.

Dr Ronald M Lazer [38] et al performed a study on patients having TIA by giving a sedative dose of midazolam. These patients did not undergo any surgery. In this study, four right-handed patients participated. Three of them had clinical TIA that was presumed to have affected the left hemisphere within the previous 24 to 72 hours. There was no evidence of a new lesion on diffusion-weighted and fluid-attenuated inversion recovery imaging. One patient had an asymptomatic temporal arteriovenous malformation. This study shows that, patients who had suffered recent transient cerebral ischemic episodes and were neurologically intact with negative diffusion-weighted imaging showed re-emergence of prior focal deficits after administration of a benzodiazepine in a dose that produces light sedation. These findings suggest that presumed TIA may produce neuronal dysfunction beyond the symptomatic period.

Schubert, Armin MD [39] et al performed a study on effect of cranial surgery and brain tumor size on emergence from anaesthesia. They compared anaesthetic emergence

from complex spinal surgery (spine; n = 47) with that from craniotomy for supratentorial nonfrontal (n = 22), frontal (n = 34), or posterior fossa tumour (n = 28). A further comparison involved patients with small versus large (diameter > 30 mm, mass effect) tumours. In this study, the IV drugs used were thiopentone and sufentanyl. The inhalational agents used were isoflurane and nitrous oxide. This study showed that craniotomy patients performed less well than spinal surgery patients on the mini neurologic examination 15 and 30 min after discontinuing nitrous oxide. At 15 min, fewer patients with large (vs. small) tumours were oriented to time (58% vs. 87%; $P < 0.01$) or place (67% vs. 90%; $P < 0.01$). Forty-two percent of patients with large tumours still had an abnormal mini neurologic examination score versus 15% of patients with small tumours. At 30 min, these values were 28% and 8%, respectively ($P < 0.05$). Seventy-one percent of patients with large tumours were oriented to time compared to 97% for small lesions ($P <0.01$). Emergence from anaesthesia was similar for spinal surgery patients and patients with small brain tumours. In conclusion, patients undergoing craniotomy for large intracranial mass lesions awaken more slowly than patients after spinal surgery or craniotomy for small brain tumour.

J.Pouttu [40]et al conducted a study to know the effect of clonidine (4.5 μg kg-1) on haemodynamics and hormonal stress in 21 female patients undergoing breast surgery. In this study, the standardized general anaesthesia included diazepam as premedicant, thiopentone, enflurane, N_2O, fentanyl and vecuronium. Venous plasma concentrations of noradrenaline, adrenaline, growth hormone, vasopressin, and cortisol were assayed at various times before, during and after surgery. Clonidine attenuated the sympatho-adrenal response; arterial blood pressure and heart rate increases in association with intubation were lower in clonidine-premedicated patients. Noradrenaline levels were lower throughout and 3 h after surgery in the clonidine group ($P<0.05$). Adrenaline

levels were lower in this group 2 min after intubation ($P<0.05$). Growth hormone, vasopressin and cortisol plasma levels were increased at the end of and after surgery, with no differences between the groups. In spite of the effect on sympatho-adrenal response, clonidine did not have any significant additive anxiolytic effect. Statistically significant differences were not found as to need for postoperative analgesics.

Krechel, Susan W et al [41] have reported two cases of nalaxone causing beneficial effect in patients having previous focal neuro logical deficits. The first was an unexpected, complete resolution of an acute unilateral neurologic deficit associated with anaesthesia when naloxone was administered to reverse residual narcotic effect. The second was a complete resolution of postoperative unilateral electroencephalographic evidence of ischemia after naloxone administration in a patient following a carotid endarterectomy. A literature search suggests that naloxone may be useful in the treatment of acute and hyper acute stroke due to ischemia. Transient focal neurologic deficits have been observed in patients emerging from brain tumour or carotid surgery, and a pharmacologic effect of anaesthetic agents has been proposed as the cause of such neurologic dysfunction. Therefore, the effect of sedation with midazolam or fentanyl on motor neurologic function was studied by Thal GD et al [2] prospectively and preoperatively in patients with carotid disease or mass lesions of the brain. This study was done in 54 unpremedicated adult patients with carotid disease or brain tumour.

The IV anaesthetic drugs used in this study were midazolam and fentanyl. A thorough motor examination was performed at baseline and after sedation by an individual who was unaware of the details of the patient's disease or symptoms. A mental status examination also was performed to control for the effects of inattentiveness or lack of

cooperation during the neurologic examination. This study shows that patients were sedated mildly but were fully cooperative. Focal motor deterioration occurred after sedation in 30% of patients, and the incidence was similar in patients in the fentanyl and midazolam groups. Among patients with a focal motor abnormality on baseline examination or a resolved prior motor deficit, 73% had exacerbation or unmasking of these signs by sedation, whereas no patient without a prior history of motor dysfunction had a sedative-induced change. Sedative-induced changes in neurologic function ranged from unilateral mild weakness to complete plegia, but appeared to be transient in nature. In conclusion, sedation with midazolam or fentanyl can transiently exacerbate or unmask focal motor deficits in patients with prior motor dysfunction.

Method of examination of normal motor power

Normal motor power can be examined by inspection, palpation examining for power and eliciting deep tendon reflexes. The upper extremity muscles are inspected for bulk and fasciculations. The muscle tone is assessed by putting selected muscle groups through passive range of motion. The most commonly used maneuvers used for the upper extremity are flexion and extension at elbow and wrist. Muscle strength is tested from the proximal to the distal part of the extremity so that all the segmental levels for the extremity are tested.C5-Shoulder extension, C6- Arm flexion, C7-Arm extension, C8-Wrist extension, T1-Hand grip. The levels for deep tendon reflexes- Biceps- C5, C6, Brachioradiolis – C5, C6, Triceps- C7.

Similarly Lower limb muscles are inspected for bulk and fasciculation. Muscle tone is assessed by putting selected muscle groups through massive range of motion. Muscle strength is tested from the proximal part to distal part so that all segmental levels are tested. Segmental levels of lower limb are L2-Hip flexion, L3 –knee extension, L4-Knee flexin, L5 –Ankle dorsiflexion and S1-Ankle plantar flexion.

Levels for DTR in the lower limb are - Patellar or Knee-L2,L3 and Ankle –S1,S2.

Muscle strength grading is done as follows-

0-when there was no movement.

1-when there was a flicker of movement.

2-when there was movement with gravity eliminated.

3- When movement against gravity.

4- Less than normal power.

5- Normal power.

Method of examination of mild motor deficits.

Patients with mild corticospinal tract (CST) [42] lesions may have normal strength to routine testing but the neurological deficit may be brought out using ancillary maneuvers. The most important of these is the examination of the pronator drift (Barre's sign). This sign is elicited in the following way-With the patients upper extremities outstretched to the front, palms up and the eyes closed, the position of each extremity is observed.

In normal patients, the palms will remain flat, the elbows straight and the limbs horizontal. Any deviation from this position will be similar on both sides. The patient should hold this position for 20-30 seconds.

The patient with a mild CST deficit may demonstrate pronator drift to varying decrees. With mild drift, there is a slight pronation of the hand and slight flexion at the elbow on the abnormal side.

With more severe drift, there is more prominent pronation and obvious flexion of the elbow and there may be down ward drift of the entire arm. Due to the innervation

pattern of the CST, the minimally weak CST innervated muscles are overcome by the non CST muscles. With a mild CST lesion, the minimally weak muscles in the upper extremity are the extensors, supinators and abductors. These are overcome by the uninvolved and therefore stronger muscles, i.e. the pronaters, biceps and internal rotators of the shoulders these overcome the slightly weakened CST innervated muscles, the hand pronates, the elbow flexes and the arm drifts down wards.

Another sign occasional useful is the “Digiti Quinti” sign. With the hands outstretched in drift position, the small finger on the hemi paretic side may be abducted more than on the normal side.

If only motor test could be done on a patient, the best single test to use would probably be examining for drift.

The examiner may hasten the development of drift by tapping on the palms or having the patient turn the head back and forth. The examination for drift is often combined with Romberg’s test, since both require the patient to have eyes closed.

Other useful maneuvers include examination of the forearm roll and rapid alternating movements.

Abnormal fore arm rolling is a sensitive indicator of neurological pathology. To test it, the patient is instructed to make fists and hold the forearm horizontally so that the fists and distal fore arm overlap with the palms pointing more or less towards the umbilicus and then to rotate the fists around each other first in one direction and then the other .Normal patients will have about an equal excursion of both forearms, so that the fists and forearm roll about each other symmetrically. With a unilateral corticospinal lesion, the involved side does not move as much as the normal side.

Finger roll is an even more sensitive version of the same test. The patient is asked to extend the fore finger from the clenched fists and to rotate the finger around each

other, moving just the fingers. Again, the finger on the abnormal side will move less than its fellow.

Fine motor control may be tested in numerous ways .The patient may be asked to repetitively and as quickly as possible touch the tip of the index finger to the tip of the thumb. The movements will be slower and less agile on abnormal side.

Similar procedures can be used to detect lower extremity weakness. The examination for leg drift is possible but is not nearly as useful as testing for arm drift.

In the leg or knee dropping test, the patient lies supine with the hips and knees flexed, the knees forming an angle of about 45 degrees and the heels resting on the table. When a CST lesion is present, the affected heel will gradually slide downwards so that, the knee slowly extends and hip goes into extension, external rotation and abduction.

Fine motor control of the foot can be assessed by having the patient do rapid repetitive foot taps on the floor if standing and against the examiners' palm if supine.

Incidence of motor deficits

Mukand et al [43]conducted a study to study the incidence of Neurologic deficits. He did a retrospective, descriptive study to discuss common neurologic problems in adults with brain tumours admitted for inpatient rehabilitation at an acute rehabilitation centre. In this study, the most common deficit was impaired cognition (80%), followed by weakness (78%), visual-perceptual deficit (53%), sensory loss (38%), and bowel and bladder dysfunction (37%). Less common problems, in decreasing incidence, were cranial nerve palsy, dysarthria, dysphasia, aphasia, ataxia and diplopia. Thirty-eight (74.5%) patients had three or more concurrent neurologic deficits, and 20 (39.2%) patients had five or more deficits. Concurrent deficits among patients with hemi- and quadriparesis involved cognition (n = 29 patients), visual-

perceptual function, sensation, cranial nerve palsy, and neurogenic bowel/bladder. Impaired cognition, weakness, and visual-perceptual deficits were the most common problems in this study population. This study supports the benefits of comprehensive and interdisciplinary rehabilitation for patients with primary as well as metastatic brain tumours. It is important to follow up patients post operatively in order to follow the prognosis. CT scanning done to follow the prognosis of chronic subdural Haemorrhage patient shows that, true re accumulation of haematoma occurs in 45% of patients after burr hole. Other complications include subdural empyema, brain abscess and meningitis. These complications occur in less than 1% of patients. Seizures are reported in 10% of cases.

Alex Macario et al did a metaanalysis of trials comparing post operative recovery after anesthesia with sevoflurane and desflurane. Results of published, randomized controlled trials comparing sevoflurane and desflurane were pooled to measure differences in times until patients obeyed commands, were extubated, were oriented, were discharged from the post anesthesia care unit (PACU), and were ready to be discharged to home, as well as the occurrence of postoperative nausea and vomiting (PONV). Twenty-two reports of 25 studies (3 reports each described 2 studies) met our inclusion criteria. A total of 746 patients received sevoflurane, and 752 received desflurane. This Meta-analysis of studies in which the duration of anesthesia was up to 3.1 hours, indicated that patients receiving either desflurane or sevoflurane did not have significant differences in PACU time or PONV frequency. Patients receiving desflurane followed commands, were extubated, and were oriented 1.0–1.2 minutes earlier than patients receiving sevoflurane.

Muzzi et al did a study on the effect of desflurane and isoflurane on cerebrospinal fluid pressure in humans with supratentorial mass lesions. This study was conducted in twenty adult patients undergoing craniotomy for removal of supratentorial mass lesions. The anaesthetic agents used in this study were isoflurane, desflurane, thiopentone and vecuronium. This study showed that there was no difference in the mean (+/- SD) awake CSFP between the desflurane (11 +/- 4 mmHg) and the isoflurane (10 +/- 2 mmHg) groups. Turner CR et al did a study to know brain relaxation and cerebrospinal fluid pressure during craniotomy for resection of supratentorial mass lesions. This was retrospective study of 32 patients who had undergone elective craniotomy for resection of supratentorial mass lesions. The anaesthetic agents used in this study were isoflurane, desflurane and nitrous oxide. This study showed that in patients undergoing elective craniotomy for resection of a supratentorial mass lesion, tight brain occurred with a lower frequency in patients receiving 0.5 MAC Isoflurane or Desflurane with 50% N2O than in patients who received 1 MAC Isoflurane or Desflurane.

METHODOLOGY

This study was a prospective, double-blinded randomized controlled trial comparing the effects of 2 inhalational anaesthetic agents - desflurane and isoflurane with regard to emergence and recovery of early neurological deficits in patients undergoing supratentorial craniotomy. Our hypothesis was that desflurane caused quicker emergence from anaesthesia and faster recovery from an early post-operative neurological deficit compared to isoflurane. The sample size initially chosen was 60 (18 – 70 years, ASA I-III) patients (30 patients in each arm) undergoing elective neurosurgery for supratentorial mass lesions.

Inclusion Criteria for the study in elective neurosurgical patients with supratentorial intra-axial mass lesions was

a. Age 18 -75 years

b. ASA Grade 1-3

c. Pre-operative GCS – 15/15

The exclusion criteria was

a. Previous craniotomy

b. Hepatic or renal disease (elevated SGOT/SGPT/ALP/creatinine)

c. Alcohol or drug abuse

d. Hypothyroidism– any thyroid function test outside normal limits

e. BMI > 35

f. Female patients – pregnant/breastfeeding

On the preoperative day, the patient was enrolled for study and a study number was allotted to him serially. Written informed consent was obtained from all patients enrolled in the study. The following was documented – demographic data, history of

neurological deficits, current neurological deficits, blood investigations, CT/MRI findings, and current medications. Each patient received 3mic/kg of Tab. Clonidine as premedication. The patient was instructed that he/she would be asked some questions and some tests will be done immediately after waking up from anaesthesia and his co-operation was requested. Each patient entering the study was assigned a study number and was randomized into either group.

i. **Method of randomization:**

Block randomization- 10 blocks of 6 patients in each block. Each study number was randomly allocated to either desflurane or isoflurane group.

ii. **Method of allocation concealment:**

Each patient had a study number. Envelopes with the study numbers on it were prepared by the statistician with the name of the inhalational agent (desflurane or isoflurane) written on a paper inside. The envelopes were kept in the Neuro theatre in the technician's cupboard. The envelope was accessed by the anesthetist before induction on the day of the surgery.

Blinding and masking:

This study was a double-blinded trial. The patient was unaware of what anaesthetic agent was being administered to him/her. A fellow anaesthetist or neurosurgical registrar assessed the patient during recovery unaware of the inhalational agent that was administered.

The choice of anaesthetic agent to be used was known only on the day of surgery. All the patients received induction with propofol, fentanyl and vecuronium and maintenance of anaesthesia was according to study guidelines. The inhalational agent

– desflurane or isoflurane- was decided as per the randomization. Intra-operative monitoring of patient hemodynamic and physiological parameters was done.

Materials and drugs used for the study:

Isoflurane vaporizer, desflurane vaporizer, Philips MP-50 Monitor with PPV, ETCO2 and temperature monitoring, arterial blood pressure kit, infusion pump , nerve stimulator, propofol, fentanyl, vecuronium, Perfalgan, Diclofenac Ampoules and Xylocard.

On the day of surgery, the patient was received at the theatre receiving area and taken inside by the anaesthetist. The envelope corresponding to the study number was taken from the anaesthesia cupboard. The appropriate vaporizer was brought inside the theatre. A central venous access was secured under local anaesthesia and radial artery cannulation was also done under local anaesthesia. After recording the haemodynamic and physiological parameters on display the patient was anaesthetized.

The protocol used was as follows.

INDUCTION- Propofol 2 mg/kg was used for induction.1mg/kg of Xylocard was given before intubation .Total Fentanyl given was 3mcg/kg.-1mcg/kg at induction,1mcg/kg just before intubation and 1mcg/kg just before making burr hole or drilling. Vecuronium 0.15mg/kg was given at induction. Vecuronium infusion was titrated to two twitches after induction. Intravenous paracetamol 1 gm was infused for all cases after induction and before incision.

MAINTENANCE: MAC for both desflurane and isoflurane was maintained at 0.8.Intraoperative monitoring of arterial blood pressure, ETCO2, PPV (Pulse Pressure Variation)

The **brain relaxation score** was assessed as follows:

1- Relaxed brain.

2- Mild brain swelling.

3- Moderate brain swelling, no treatment required.

4-Severe swelling, treatment required.

Variation), Temperature, ECG, SPO2, Heart rate was done and documented. Surgeon was asked to assess the brain relaxation score at opening of Dura. Raised blood pressure was controlled using labetalol or metaprolol. Intraoperatively, a mean blood pressure of 60-65 mmHg was maintained. Number of hypertensive, hypotensive episodes that occurred was noted. Diclofenac 75mg/kg was added to the infusion at the time of dural closure. Vecuronium infusion was stopped when skin closure began. Inhalational agent was stopped without tapering once the head was removed from pins. Fresh gas flow of 100% oxygen was raised to 8litres/min. The patient was extubated at purposeful movement or cough without any external stimulation, if neuromuscular recovery was ascertained by satisfactory response to double burst stimulation and respiration was considered adequate. Arterial blood gas samples were taken for all patients to document electrolyte and blood gas levels. Dosages of each anaesthetic agent were documented. The time at induction to stopping of anaesthetic agents and reversal was noted.

After discontinuing anaesthesia, the anaesthetist noted the time to extubation and eye opening. A mini-neurological examination, which assessed motor response and orientation, was done every 2 minutes till full recovery.

Time to eye opening, time to extubation, time of obeying motor commands, time when oriented, time when motor deficits were detected were examined and documented. Duration of Time of Eye opening was calculated as duration of time from discontinuation of inhalational agent to opening of eyes either spontaneously or on verbal prompting repeated every minute. Duration of time of extubation was calculated from time of discontinuation of inhalational anaesthetic to time of extubation. Time of obeying motor commands was noted when patient obeyed one of the following commands- show tongue; lift hand/legs, checked every two minutes. The duration of time taken to obey motor commands was calculated from time of discontinuation of inhalational agent to obeying one of the commands.

The patient was considered oriented when he gave correct answers to questions such as.-What is your name, what is the name of the hospital you are in etc.?

Early motor neurological deficits, if present, after surgery was assessed every half an hour for first 2 hours and hourly after that by the Neuro ICU registrar/sisters till recovery(maximum 12 hours).

METHOD OF EXAMINATION

We started examining the motor power of muscle groups as soon as they started obeying motor commands. We examined the power at ankle, knee, hip, wrist, elbow and shoulder joints.

We graded the power as follows according to MRC Grading-

0-when there was no movement.

1-when there was a flicker of movement.

2-when there was movement with gravity eliminated.

3- When movement against gravity.

4- Less than normal power.

5- Normal power.

Motor power of plantar flexion and dorsiflexion was tested at ankle joints. Motor power of flexion and extension was tested at knee joints, elbow and shoulder joints. When decreased power was detected, the site and time were documented. The same examination was repeated every 30 minutes by the ICU Registrar and documented. The improvement if any was documented.

Data were entered into Epi Info 3.5.1 (CDC, Atlanta, GA), and analysed using SPSS 20.0 (Chicago, IL). Since the outcome variables were not normally distributed, time durations were presented as medians with 95% CI and the Mann-whitney U test was used to compare the two groups. Student t test was used to compare normally distributed variables. Subgroup analysis was performed based on tumor size and duration of surgery. Statistical significance was set at $P < 0.05$.

RESULTS

Fifty-one patients were recruited for the study. Three patients were enrolled but not included for analysis. Of these, one patient did not receive the assigned inhalational agent, another was not extubated at the end of surgery as requested by the surgeon and the third patient developed ectopics at the end of the surgery and received additional doses of lignocaine that affected the recovery. Therefore for the analysis, 25 Desflurane patients and 23 Isoflurane patients were considered.

The preoperative and clinical data for both groups is shown in Table 1

	Desflurane	Isoflurane	P value
Number of patients enrolled	27	24	
Number of patients included for analysis	25	23	
Sex (M:F)	20:5	19:4	
Age	37.5±2.9	40.4±2.6	0.47
BMI	23.5±0.7	24.1±0.8	0.58
Preoperative creatinine	1.0±0.04	0.9±0.04	0.06
Tumor location			
Frontal	4	7	
Temporal	6	6	
Parietal	8	5	
Occipital	2	-	
Insular	4	4	
Others*	1	1	
Tumor size#	4.5±0.3	5.1±0.4	0.32
ASA grade (1:2)	15:10	17:6	

#Maximum tumor diameter in cm

*Desflurane group – parasagittal meningioma, isoflurane group – septal glioma

This preoperative, demographic and clinical data showed no significant difference between the two groups.

Table 2.Definition of Outcome variables

The parameters we studied were time to eye opening, time to extubation, time to obeying motor commands, time to orientation and time to recovery of motor deficits. The table shows the definition of the parameters.

	Parameter	Definition
1	Time to eye opening (emergence)	Time to opening of eyes spontaneously or on verbal prompting every 2 minutes.
2	Time to extubation	Time to extubation of patient.
3	Time to obeying motor commands	Time from discontinuation of inhalational agent to obeying any one of the following commands – show tongue/lift arms/squeeze fingers/lift legs. This was checked every 2 minutes.
4	Time to orientation	Time to correctly answering both of the following questions: a. What is your name? b. What is the name of the hospital you are in? This was checked every 2 minutes.
5	Time to motor deficit	Checked every 2 minutes once patient was extubated

Table 3: Intraopeartive Data and Fentanyl requirements

	Desflurane (n=25)	Isoflurane (n=23)	P value
Duration of surgery (minutes, mean±SE)	307.1±21.7	271.3±20.2	0.23
Brain relaxation score (median [95% CI])	2 (1.5-2.2)	1 (1.4-2.2)	0.90
Patients with bradycardia	1	2	
Patients with hypotensive episodes	6	6	
Patients with hypertensive episodes	2	4	
Total fentanyl dose (mcg)	180 (156-189)	200 (176-202)	0.11
Fentanyl dose (mcg/kg/hour)	0.63±0.04	0.73±0.06	0.19

* P <0.05, Mann-Whitney U test

All outcome variables are presented as median values and the 95% CI are within parenthesis

This table shows that there is no significant difference in duration of surgery, Brain Relaxation score and fentanyl consumption between the two groups.

Table 4. Intra operative recovery variables.

	Desflurane (n=25)	Isoflurane (n=23)	P value
Time to eye opening (minutes)	9 (8.1-13.2)	14 (13.7-20.2)	0.003*
Time to extubation (minutes)	6 (4.8-8.0)	6 (5.8-11.0)	0.35
Time to obeying commands (minutes)	12 (10.5-18.0)	20 (16.5-23.3)	0.005*
Time to orientation (minutes)	18 (14.4-21.0)	29 (23.7-33.1)	<0.001*

* P <0.05, Mann-Whitney U test

All outcome variables are presented as median values and the 95% CI are within parenthesis

This table shows the outcome variables for patients in both groups. Patients who received Desflurane had a 35.7%, 40% and 37.9% reduction in time to eye-opening, obeying commands and orientation respectively. No reduction in time to extubation was observed between the two groups. There were no differences in the recovery variables between sexes in either group (p>0.05). The incidence of prolonged extubation (> 15 min after stopping the inhalational agent) was

significantly higher among patients who received isoflurane (Chi-square test,

p=0.006) (Figure 1). Correlations between duration of surgery and time to emergence and extubation were not significant for either desflurane (p=0.27 and p=0.16 respectively) or isoflurane (p=0.28 and p=0.40 respectively).

Table. 5 :Comparison of surgical times and outcome variables depending on tumour size.

	Desflurane (n=25)			Isoflurane (n=23)		
	≤ 4cm	> 4cm	P value	≤ 4 cm	> 4cm	P value
Number of patients	13	12		11	12	
Age	38±4.2	37.0±4.2	0.88	42.0±4.2	39±3.4	0.57
Mean duration of surgery (minutes±SE)	297.8±40.5	308.3±17.1	0.81	270.1±30.6	272.4±28.0	0.95
Total fentanyl dose (mcg)	180.7±11.5	172.0±9.1	0.56	176.3±8.6	202.0±8.5	0.04*
Fentanyl dose (mcg/kg/hr)	0.68±0.07	0.58±0.03	0.26	0.69±0.09	0.77±0.09	0.58
Time to eye opening (minutes)	8 (6.1-14.4)	11.5 (7.5-14.6)	0.43	14 (10.0-17.1)	18 (14.8-25.3)	0.05
Time to extubation (minutes)	7 (5.3-9.2)	4.5 (2.8-8.2)	0.13	5 (3.9-6.5)	10.5 (6.9-15.9)	0.02*
Time to obeying commands (minutes)	11 (7.6-21.6)	15.5 (10.4-17.3)	0.53	16 (11.5-21.3)	22 (18.7-27.6)	0.05
Time to orientation (minutes)	18 (12.8-24.5)	18.5 (12.8-20.4)	0.89	29 (16.7-32.1)	30 (26.0-38.1)	0.23

P <0.05

All outcome variables are presented as median values and the 95% CI are within parenthesis. The impact on the tumour size on emergence and extubation is shown in table 5.Significant delays in time to extubation and time to obey commands were noticed in patients with tumor size >4 cm in the Isoflurane group only.

We studied relationship between Fentanyl dose requirements and time to recover post operatively in patients with preoperative neurological deficits in both the groups.

TABLE 6. Preoperative and postoperative neurological status in patients enrolled in the study

	Desflurane (n=24)	Isoflurane (n=23)	P value
Patients with preoperative neurological deficits	3	6	
Duration of deficit (months)	8 (2-24)	1.5 (1-4)	
Patients with postoperative deficit	4	9	
Fentanyl dose in patients with deficits (mcg/kg/hr)	0.50 (0.37-0.89)	0.64 (0.44-0.87)	0.28
Patients with complete recovery	3	8	
Time to recovery (hours)	2 (1-6)	1.25 (1-4)	0.63

All durations represent median values and the range is within parenthesis.

This table shows that there is no difference in time to recovery postoperatively between the two groups. There is no significant difference in the fentanyl dose requirements in patients with motor deficits between the two groups.

We studied relationship between tumour size ,median fentanyl dose consumption , time to eye opening and time to extubation in patients with post op deficits and no post op deficits.

.

Table 7. ***Relation ship between postoperative deficit and tumor size (n=47)***

	Postop deficit absent	Postop deficit present	P – value
Tumor </= 4 cms	19	5	0.28
Tumor > 4 cms	15	8	
Median fentanyl dose (mcg/kg/hr)	0.71+/-0.05	0.63+/-0.04	
Time to eye opening	13 (3-30)	14 (3-37)	0.48
Time to extubation	5.5 (2-25)	6 (3-21)	0.24

This table shows that there is no difference in median fentanyl dose consumption, tumour size, time to eye opening and time to extubation between the patients with post op deficits and patients without any post op deficits.

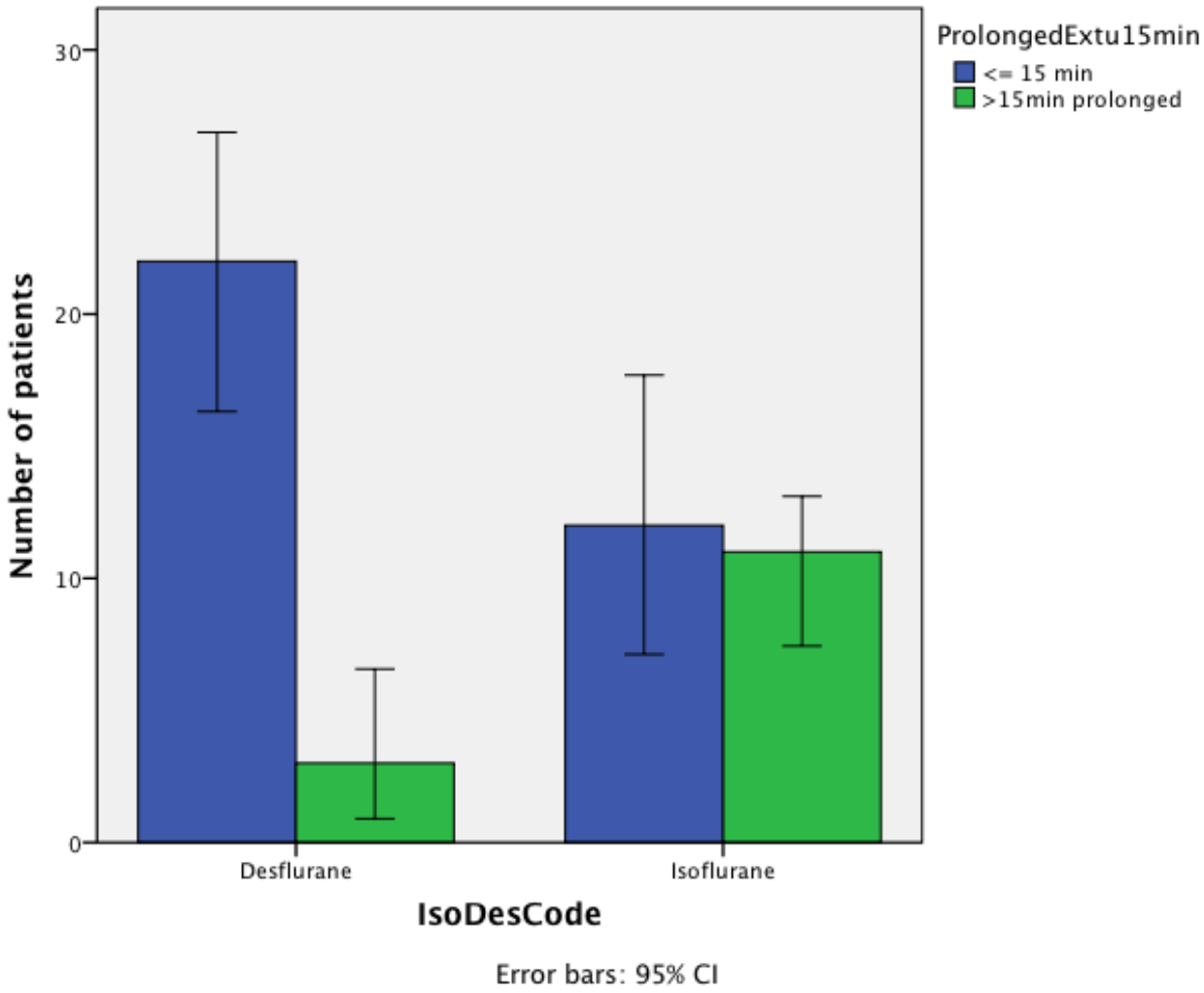
We studied relationship between hypotensive episodes and post op deficits and no post op deficits.

Table 10.Association between hypotensive episodes and postoperative deficit *(p=0.20)*

	Postop deficit absent	Postop deficit present
Hypotensive episode absent	27	8
Hypotensive episode present	7	5

This table shows that there is no significant difference between the episodes of hypotension and post op deficits.

Figure 1.Prolonged extubation



This figure shows that in desflurane group, the patients with extubation time less than 15 and more that 15 minutes were 22 and three respectively.

In Isoflurane group, patients with extubation time less than 15 minutes and more than 15 minutes were 12 and 11 respectively.

Correlation between duration of surgery and time to awakening for both groups (Kendall's tau):

Desflurane group:

No correlation between duration of surgery and time to eye-opening (p=0.27) or time to extubation (p=0.16)

Isoflurane group:

No correlation between duration of surgery and time to eye-opening (p=0.28) or time to extubation (p=0.40)

No correlation between fentanyl dose (mcg/kg/hr) and time taken to recover from postoperative deficit (all cases, n=11): p=0.05.

No correlation between duration of surgery and time taken to recover from postoperative deficit (all cases, n=11): p=0.07

Time taken to recover from neurological deficits did not correlate with either the duration of surgery (Kendall's tau= 0.56, p=0.07) or the fentanyl dose (mcg/kg/hr) (Kendall's tau=-0.47, p=0.05).

DISCUSSION

Our study showed that patients on desflurane had significantly faster awakening with regard to time to eye opening, obeying commands and orientation. This can be explained by the longer residual effect of isoflurane on higher cognitive function. Response to command occurs after anaesthesia comes down to a much smaller end tidal concentration than MAC awake. However time to extubation was similar in both groups. Our criterion for extubation in this study was purposeful movements or cough without any external stimulation, provided patients were breathing adequately. This was done to ensure as smooth an extubation as possible without rise in BP and ICP. However we kept the patients under observation till they obeyed commands and were oriented to time and place.

Previous studies have compared desflurane and isoflurane with regard to emergence and extubation times in variety of non-neurosurgical procedures. Kaye et al.,[9] studying the impact of desflurane and isoflurane on lumbar CSF pressures in patients with intracranial tumors, also documented emergence times after supratentorial craniotomies. Although the authors found that patients who received desflurane (n=18) were able to open their eyes and obey commands in 50% less time than those who received isoflurane (n=18), the differences were not significant. The authors attributed these results to the small sample size, duration of surgery and anesthetic protocol. Previous studies have shown that when eye opening is considered criterion for extubation, desflurane can reduce extubation by about 34% and sevoflurane by 27%. In a more recent study by Yildiz et al[47] . 50 patients received 1 MAC of either desflurane or isoflurane during supratentorial craniotomy for tumors/aneurysms. Patients who received desflurane had shorter eye-opening, extubation and orientation times. The results from the above two studies were remarkably divergent in terms of the actual

recovery times (time to eye-opening 30 minutes and 4.3 minutes respectively). While differences in anesthetic protocol may have contributed to this result, the rapid extubation time (1.98 minutes) in the study by Yildiz et al. has not been shown in other neurosurgical series using desflurane.

Rapid emergence is desirable in neurosurgical patients to rule out any potential surgical cause for impaired neurological recovery. More than 15 min is generally considered delayed recovery. Patients in the desflurane group were all oriented to time and place before 30 min. Other studies have also documented that the quality of recovery is different for the two agents, particularly with regard to psychomotor function. Although we did not determine the quality of recovery in our series, we noticed that patients receiving isoflurane were drowsier and showed inconsistent responses to stimulation, while patients receiving desflurane were more alert. Also, shorter time to orientation meant that in addition to motor deficits, speech and language functions could also be assessed earlier. This could be important, especially, for tumors around the language area in the dominant hemisphere.

We also looked to see if the tumour size had any influence on awakening. We found that those who had a tumour size more than 4 cm in the isoflurane group took longer time for extubation. However the tumour size did not have any impact on the desflurane group with regard to time to extubation. The duration of surgery was longer in patients who had tumour size more than 4 cm in the desflurane group. This was not so in the isoflurane group. Despite this the extubation time was significantly longer in the isoflurane group.(p 0.02) The time difference for eye opening and obeying commands also was longer in the isoflurane group. This difference was nearly significant (p 0.05). Previous reports have shown that patients with tumors > 3cm had a more gradual emergence as compared to patients with smaller tumors or those undergoing spinal surgery.[39,48] Authors have suggested that the brain shift

associated with large intracranial lesions[49] as well as traction and pressure on the reticular activating system during surgery can result in depressed consciousness. Grover et al. showed that tumor location also affects emergence, in that frontal and posterior fossa tumors were associated with delayed awakening. In our series, we selected only patients with supratentorial tumors and the number of patients with frontal tumors >4cm (n=5) and ≤4 cm (n=6) was similar. While other factors including age, hyperventilation and electrolyte disturbances are known to affect emergence, these were not different between the two groups in our series (Table 5). Desflurane may be advantageous since it provides rapid recovery irrespective of tumor size or surgical duration. Moreover, the excision of large infiltrating tumors is associated with a higher chance of damage to eloquent areas in the brain and desflurane allows for an early postoperative neurological examination.

Schubert Armin[39] et al have also shown that patients undergoing craniotomy had fared poorly on mini neurological examination as compared to complicated spinal surgery 15 to 30 min after surgery and patients with large tumours more than 30 mm had delayed awakening. Different mechanisms have been suggested for this. Lossaso[45] et al considers the degree of brain exposure in the operative field to have an effect on the recovery. Brain tissue shift is also considered to be responsible for depression of consciousness. Surgical intervention, brain tissue dehydration, hyperventilation have all been thought to cause relative shift in the immediate post period. Another possible explanation is when large brain tumours are removed, the edema may lead to slower washout of anaesthetic agents. Intravenous agents may also diffuse into the brain tissue causing delayed excretion.

Reversible neurological deficits

There were 4 patients in the desflurane group and 9 patients in the isoflurane group who had some postoperative motor deficit. It is a common observation in the immediate postoperative period that spontaneous movement of extremities is delayed on the opposite side of operation after supratentorial craniotomy and the on the same side after posterior fossa surgery. Majority of neurological deficits after surgery recovers over time, but this time period is unpredictable. The exact mechanism for this is unknown. It has not been established if this is related to surgery or anaesthesia. If it is anaesthesia related, early awakening may shorten the deficit duration and can avoid unnecessary radiological investigation. However our study failed to show any correlation between faster awakening from anaesthesia and improvement in motor deficit. Patients with deficit may have been too small for a meaningful comparison.

The administration of benzodiazepines or opioids has been shown to induce worsening/reappearance of pre-existing motor deficits[2, 37, 50, 51]. A number of mechanisms have been proposed to explain this phenomenon. Firstly, the disruption of the blood brain barrier in and around the tumor may alter drug uptake and metabolism. Secondly, neurons around the tumor may be partially damaged and hypersensitive to centrally acting anesthetic agents. Thirdly, anesthetic agents may impact signal transmission in certain neuronal circuits around the tumor creating detecta1ble deficits. While none of these theories have been proven, the use of naloxone to reverse deficits induced by opioids, suggests that the central action of these drugs has a role to play.[41,52] The potential role of inhalational anesthetic agents in producing such deficits has not been explored to date. In our study, 11 of 13 patients developed postoperative motor deficits that recovered within 12 hours. Patients of both groups received similar doses of opioids, did not sustain any operative complications, and had no significant metabolic abnormalities at the end of surgery. Although, we found no significant

difference in the time to neurological recovery in both groups, our data demonstrates that reversible neurological deficits manifest after intracranial surgery and need to be acknowledged when evaluating the postoperative patient. While we cannot conclude that the anesthetic agent contributed to the neurological deficits, the restricted use of opioids and the use of short-acting anesthetics definitely allowed for the earlier evaluation of these patients. Although some authors have suggested that short-acting anesthetic agents for neuroanesthesia may reverse these deficits faster,[53] more studies are required to justify the use of desflurane for this purpose.

Pharmacokinetics and cost

The blood: gas and brain: blood partition co-efficient of desflurane are lower than that of isoflurane.[53] Keeping other variables constant, this translates into faster emergence from anesthesia when using desflurane. The time to recovery is less affected by the duration of anesthesia when using low soluble anesthetics such as desflurane,[25] and this is particularly useful in long duration surgeries such as neurosurgery. Increased lumbar CSF pressure has been attributed to desflurane in animal[54,55] and human studies[45] previously. However, recent studies have shown no significant difference between the effects of desflurane and isoflurane on intracranial pressure (ICP) and cerebral perfusion pressure in patients with supratentorial tumors[9, 10.] Additionally, both agents have been shown to have similar effects on cerebral blood flow in patients with intracranial mass lesions[11] . In the present study, we grossly estimated the intracranial pressure using a brain relaxation score. Todd et al.[56] first proposed this 4-point score and found that it correlated with measured ICP. Similar to the results of Yildizet al.,[47] we found no significant difference in brain swelling between the desflurane and isoflurane groups, indicating that both agents have a similar effect on ICP in patients with large intracranial mass lesions.

With increasing efforts to reduce anesthesia-related costs, the pharmacoeconomics of desflurane still need to be considered before using it uniformly for neuroanesthesia. While the cost of using isoflurane is lower, desflurane facilitates shorter post anaesthesia care unit (PACU) durations and this has been shown to potentially offset the higher cost of desflurane, particularly, in busy operating rooms where post anaesthesia care space is limited.[57] Additionally, the use of low-flow anesthesia can reduce the consumption and costs of using desflurane. In the present study, since extubation times were similar with both agents, we believe the use of desflurane be restricted to long-duration craniotomy cases where early cognitive and neurological assessment is crucial. Other authors have made similar recommendations for the use of desflurane, since the efficient use of isoflurane and opioids can produce comparable recovery times with lower expenditure.[58, 59]

Limitations of the study

The number of patients with motor deficits is too small to come to any meaningful conclusion recommending use of desflurane to reduce neurologic deficit. .

Conclusions

1, Desflurane has a faster awakening with regard to eye opening, obeying commands and orientation.

2. Desflurane is useful in long duration surgeries with large tumours where early neurological examination is required.

3. Inhalational anaesthetic agent has no significant effect on neurological deficit.

Bibliography

1. Lerman J, Gregory GA, Willis MM, Eger El 11. Age and solubility of volatile anesthetics in blood. Anesthesiology 1984;61: 139-43.

2.Thal GD, Szabo MD, Lopez-Bresnahan M, et al. Exacerbation or unmasking of focal neurologic deficits by sedatives. Anesthesiology. 1996; 85: 21-5.

3 Lerman J, Gregory GA, Eger **.** Hematocrit and the solubility of volatile anesthetics in blood. Anesth Analg 1984; 63:911-4

4. Andrews JJ, Johnston RV Jr: The new Tec 6 desflurane vaporizer. Anesth Analg 76: 1338, 1993. PUBMED .

5. Hendrickx JF, De Cooman S, Deloof T, Vandeput D, Coddens J, De Wolf AM.The ADU vaporizing unit: a new vaporizer.Anesth Analg. 2001 Aug; 93(2):391-5

6. Leila G. Welborn, Raafat S. Hanalah, Willis A. McGill .Induction and recovery characteristics of desflurane and halothane anaesthesia in paediatric outpatients Pediatric Anesthesia.Volume 4, (6), pages 359–364, November 1994

7. .S. R. Wrigley, J. E. Fairfield, R. M. Jones, A. E. Black Induction and recovery characteristics of desflurane in day case patients: A comparison with propofol.Anaesthesia Volume 46 (8), pages 615–622, August 1991

8. Visser, Klazina M.D.; Hassink, Elly A. et al Randomized Controlled Trial of Total Intravenous Anesthesia with Propofol versus Inhalation Anesthesia with Isoflurane-Nitrous Oxide: Postoperative Nausea and Vomiting and Economic Analysis .Anesthesiology: September 2001 - Volume 95 – (3) - pp 616-626.

9. Kaye A et al. The comparative effects of desflurane and isoflurane on CSF pressure in patients with craniotomy for supratentorial tumors. Anesth Analg 2004;98: 1127-32.

10. Fraga M et al. The effects of isoflurane and desflurane on intracranial pressure, cerebral perfusion pressure, and cerebral arteriovenous oxygen content difference in normocapnic patients with supratentorial brain tumors. Anesthesiology 2003;98: 1085-90.

11. Ornstein E, Young WLet al. Desflurane and isoflurane have similar effects on cerebral blood flow in patients with intracranial mass lesions. Anesthesiology 1993;79: 498-502.

12. Smiley RM, Ornstein E, Matteo RS, et al. Desflurane and isoflurane in surgical patients: comparison of emergence time. Anesthesiology 1991;74: 425-8.

13. Azad SS,Bartkowski RR,Witkowski TA. A comparison of desflurane and isoflurane in prolonged surgery. J Clin Anesth 1993;5:122-8.

14. Gerlach. Remifentanil–propofol versus sufentanil–propofol anaesthesia for supratentorial craniotomy: a randomized trial European Journal of Anaesthesiology (2003), 20 : pp 813-820

15. Ebert, Thomas J. MD,et al Recovery from Sevoflurane Anesthesia: A Comparison to Isoflurane and Propofol Anesthesia.Anesthesiology: Dec 98 - Volume 89 –(6) - p 1524–1531.

16. Agoliati A. Meta-Analysis of Average and Variability of Time to Extubation Comparing Isoflurane with Desflurane or Isoflurane with Sevoflurane Anaes Analg 2010; 110; 570-580.

17. B Larsen.Recovery of cognitive function after remifentanil-propofol anesthesia: a comparison with desflurane and sevoflurane anesthesia. .Anesth Analg (2000) Vol: 90, Iss: 1, Pages: 168-174.

18.W.Wilhelm et al.Recovery and Neurological Examination after RemiFentanyl-Desflurane or Fentanyl .BJA 86(1);44-9,2001

19. S. Gergin et al. Sevoflurane Vs Desflurane: Haemodynamic Parameters and Recovery Characteristics. The Internet Journal of Anesthesiology. 2005 Volume 9 Number 1.

20. Nathanson MH et al. Sevoflurane versus desflurane for outpatient anaesthesia: A comparison of maintenance and recovery profile. Anesth Analg 1995; 81: 1186-1190.

21. Piyush .M.Patel.Cerebral Physiology and effects of Aneasthetic drugs,7th edition,Millers Anaestheisa.Churchill Livingston Elsevier Publishers.Vol 1,2010 page 323.

22. Dupont J, Tavernier B, et al. Recovery after anaesthesia for pulmonary surgery: desflurane, sevoflurane and isoflurane. British Journal of Anaesthesia 1999;82: 355.

23.. White PF, Tang J, Wender R H et al Recovery profile, costs, and patient satisfaction for fast-track office-based anesthesia. Anesthesiology. 1999; 91: 253–61.

24. Ghour AF, Bodner M, White PF. Recovery Profile after Desflurane-Nitrous Oxide Versus Isoflurane-Nitrous Oxide in Outpatients. Anesthesiology 1991; 74: 419-424.

25. Beaussier M et al. Comparative effects of desflurane and isoflurane on recovery after long lasting anaesthesia. Can J Anaesth 1998; 45: 429-34.

26. G. R. Nordmann .Emergence and recovery in children after desflurane and isoflurane anaesthesia: effect of anaesthetic duration.Br. J. Anaesth. (2006) 96 (6): 779-785.

27. Magni G -A Comparison Between Sevoflurane and Desflurane Anesthesia in Patients Undergoing Craniotomy for Supratentorial Intracranial Surgery .Anes & Anal, Augt 2009 vol. 109 no. 2 567-571

28. Zelcer J, Wells DG. Anaesthetic related recovery room complications. Anaesth Intensive Care. 1987;15:168–74.[PubMed]

29. Anastasian ZH, Ornstein E, et al .Delayed Arousal. .Anes Clin. 2009 Sep; 27(3): 429

30. Rainer L, Elvine M, Veronika G. Et al. .Mild Intraoperative Hypothermia Prolongs Postanesthetic Recovery. Anesthesiology 1997:87 (6)- p 1318–1381

31.Bennett JA, Lingaraju N, Horrow JC, McElrath T. Elderly patients recover more rapidly from desflurane than from isoflurane anesthesia. J Clin Anesth 1992; 4:378-381

32. L. La Colla1,A. Albertin,G. La Colla and A. Mangano .Faster wash-out and recovery for desflurane vs sevoflurane in morbidly obese patients when no premedication is used.Br. J. Anaesth. (2007) 99 (3): 353-358.

33.Gupta A, Stierer T, Zuckerman R et al. Comparison of Recovery Profile After Ambulatory Anesthesia with Propofol, Isoflurane, Sevoflurane and Desflurane:; A Systematic Review Anesth Analg. 2004;98:632–41

34. Chi O Z et al . The Effects of Morphine on Blood-Brain Barrier Disruption caused by Intracarotid Injection of Hyperosmolar Mannitolin Rats. Anesth Analg 2000;90:603

35.Michael J.Sourter, Neurocritical care, 7th edition,Millers Anaestheisa.Churchill Livingston Elsevier Publishers.Vol 2,2010 page 2902-2903.

36. W. C. Cosolo et al. Blood-brain barrier disruption using mannitol: time course and electron microscopy studies. Am J Physiol February 1, 1989 256:(2) R443-R447

37. Miller R, Crosby G, Sundaram P. Exacerbated spinal neurologic deficit during sedation of a patient with cervical spondylosis. Anesthesiology 1987;67: 844.

38. Ronald M. Lazar et al .Midazolam Challenge Reinduces Neurological Deficits After Transient Ischemic Attack.Stroke. 2003; 34: 794-796

39. Schubert, et al . Effect of Cranial Surgery and Brain Tumor Size on Emergence from Anesthesia. .Anesthesiology: September 1996 - Volume 85 - Issue 3 - pp 513-521.

40. Pouttu, J., et al. (1987), Oral premedication with clonidine: effects on stress responses during general anaesthesia. Acta Anaesthesiologica Scandinavica, 31: 730–734.

41. Krechel S, Orr R, Couper N, et al. Naloxone: report of a beneficial side effect. Journal of Neurosurgical Anesthesiology 1989;1: 346.

42. Campbell. Motor strength and power.6th Edition. Dejongs Book on Nuerological examination.Lipincott and Co.2005.pp389-393.

43 . Mukand JA, Blackinton DD, Crincoli MG, Santos BB: Incidence of neurologic deficits and rehabilitation of patients with brain tumors. Am J Phys Med Rehab 2001;80:346-350.

44. Alex Macario et al .Meta-analysis of trials comparing postoperative recovery after anesthesia with sevoflurane or desflurane. Anesthesiology. 1992 May;76(5):720-4.

45.Muzzi DA et al .The effect of desflurane and isoflurane on cerebrospinal fluid pressure in humans with supratentorial mass lesions. Anesthesiology. 1992 May;76(5):720-4.

46. Turner CR, Losasso TJ et al. Brain relaxation and cerebrospinal fluid pressure during craniotomy for resection of supratentorial mass lesions. Neuro Anest. 1996 Apr;8(2):126-32.

47 Yildiz K: A Comparison of 1 Minimum Alveolar Concentration Desflurane and 1 Minimum Alveolar Concentration Isoflurane Anesthesia in Patients Undergoing Craniotomy for Supratentorial Lesions. Current Therapeutic Research 72:49-59, 2011.

48. Grover VK, Tewari MK: Cranial surgery: Impact of tumour size and location on emergence from anaesthesia. Journal of Anaesthesiology Clinical Pharmacology 23:263, 2007

49. Ropper AH: Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. The New England journal of medicine 314:953-958, 1986.

50. Benzel EC, Hadden TA: Does sufentanil exacerbate marginal neurological dysfunction? Journal of Neurosurgical Anesthe siology 2:50-52, 199050

51 Joffe AM: Transient anesthetic-induced worsening of existing left-sided weakness in a patient undergoing elective anterior cervical discectomy. Jr of Clin Anes 21:131-134, 2009..

52. Dubow J, Bernstein RA: Amplification of acute focal ischemic deficit by narcotics. Neurocritical care 8:427-429, 2008

53. Bruder N, Ravussin P: Recovery from anesthesia and postoperative extubation of neurosurgical patients: a review. Journal of Neurosurgical Anesthesiology 11:282, 1999

53. Sakai EM, Connolly LA: Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. Pharmacotherapy 25:1773-1788, 2005.

54. Lutz LJ, Milde JH, Milde LN: The cerebral functional, metabolic, and hemodynamic effects of desflurane in dogs. Anesthesiology 73:125-131, 1990

55. Lutz LJ, Milde JH, Milde LN: The response of the canine cerebral circulation to hyperventilation during anesthesia with desflurane. Anesthesiology 74:504-507, 1991.

56.Todd MM, Warner DS : A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology 78:1005-1020,

57. Beaussier M et al: Desflurane improves the throughput of patients in the PACU. A cost-effectiveness comparison with isoflurane. Can J Anaesth 49:339-346, 2002.

58. Odin I, Feiss P: Low flow and economics of inhalational anaesthesia. Best practice & research. Clinical anaesthesiology 19:399-413, 2005.

59. Weinberg L: Pharmacoeconomics of volatile inhalational anaesthetic agents: an 11-year retrospective analysis. Anaesthesia and intensive care 38:849-854

Annexures

STUDY DATA SHEET

S.No

1. Name

2. Age

3. Sex – M / F

4. Hospital Number

5. Diagnosis

Preoperative

1. History of neurological deficit - Y / N

2. If YES,

- Deficit
    - **1.** Side:
    - **2.** Limb:
    - **3.** Power:
- Duration (in months) :

3. Co-morbidities :

4. BMI :

5. Current medications :

6. GCS (orientation)

Investigations :

1. Hemoglobin
2. Creatinine
3. LFT
4. Random Blood Sugar- / AC- / PC-
5. Chest X ray
6. ECG
7. CT / MRI
    - Tumour location :
    - Tumour size :
    - Midline shift :
8. ASA Grade :

Intraoperative – ALL TIMES TO BE RECORDED FROM THE MONITOR

- Please record the following in yellow-sheet:

1. MAC values every ½ hour
2. Number of episodes of
    a. Hypotension requiring treatment (MAP > 20% of baseline)

    b. Hypertension requiring treatment (MAP < 20% of baseline)

c. Bradycardia requiring treatment (HR < 45 bpm)

3. Please ask the surgeon to document the Brain Relaxation Score on opening dura:

1 – Relaxed brain

2 - Mild brain swelling, acceptable

3 - Moderate brain swelling, no treatment required

4 - Severe swelling, treatment required

- Any Adverse Events related to the anaesthesia :

At end of surgery

- Total Fentanyl consumption:

  - Time and dose of last Fentanyl :

- Stop muscle relaxant once skin closure begins.

  - Time when vecuronium infusion stopped:

- Stop inhalational agent without tapering once the head is removed from pins or after skin closure (if pins not used).

    - Time when inhalational agent is stopped: [ ]

1. Time to eye opening: [ ]

   (Time from discontinuation of inhalational agent to opening of the eyes, either spontaneously or on verbal prompting repeated every 2 min)

2. Time to extubation: [ ]

   (Performed when patient breathing spontaneously with adequate tidal volumes and saturation and/or obeying commands)

3. Time to obeying motor commands: [ ]

   (Time from discontinuation of inhalational agent to obeying any of the following commands – show tongue/lift hands/lift legs – check every 2 minutes)

4. Time to orientation: [ ]

Time from discontinuation of inhalational agent to correctly answering BOTH of the following questions:

a. What is your name?

b. What is the name of the hospital you are in?

(CMC hospital/Vellore hospital/Vellore– acceptable)

5. Time to recovery of motor deficit:

- Time when deficit detected:

(Look for deficit immediately once patient begins to obey commands)

- Side of Deficit: LEFT / RIGHT
- Limbs:

  UPPER LIMB / LOWER LIMB / BOTH
- Facial weakness: YES / NO

  If YES, which side is weak -

  RIGHT / LEFT

After 2 HOURS, check deficit HOURLY

Time Interval	GCS	Upper Limb power (x/5)		Lower Limb power (x/5)	
		Right	Left	Right	Left
0 hour					
+ ½ hour					
+ 1 hour					
+ 1½ hours					
+ 2 hours					

INFORMED CONSENT

A prospective, randomized, double-blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of post-operative motor deficits in patients undergoing elective neurosurgery for supratentorial mass lesions.

Information sheet

You are being requested to participate in a study that compares two drugs that will be used during your surgery by the anaesthetist. Isoflurane is a drug that is routinely used for neurosurgical procedures in CMCH. In our study, we plan to compare isoflurane to another drug – Desflurane. Both are being used for neurosurgery worldwide. Desflurane has the advantage of making the patient wake up earlier after anaesthesia. We also use it but not routinely because of the higher cost. Also we plan to assess your recovery from any weakness which is seen in some patients and recovers over a time. We want to see if the anaesthetic has any effect on recovery of weakness. Desflurane will help you recover faster from anaesthesia. If recovery of any weakness is also faster with Desflurane we would like to use Desflurane routinely. We want to compare these effects of isoflurane and desflurane in patients posted for neurosurgery, like you. The study is being conducted by doctors from the Department of Anaesthesia, CMCH in conjunction with doctors from Neurosurgery.

What does participation in the study mean?

If you agree to participate in this study, you will be assigned a study number before the day of surgery. You will undergo routine treatment upto the day of surgery. In the operating room, you will be given either desflurane or isoflurane, based on previous randomization. Both drugs are administered in a similar manner by vapouriser (as a gas).

At the end of surgery, the drug will be stopped and the anaesthetist will assess how fast you wake up by asking a few questions at regular intervals. Also if you do have any weakness of the limbs after the surgery, this will be assessed periodically to look for early improvement. You will be expected to give the best response possible during assessment. The assessment will be done near the operating room for a short duration (1/2 hour – 1 hour) and maybe continued in the Neuro ICU where you will be shifted after the surgery, like routine patients.

The care after surgery will be performed by the neurosurgery team and any problems will be communicated to us. Our contact details will also be available with the staff and we will be ready to attend to any problems that you may have as a result of the study.

Can you withdraw from this study?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. However, once you are in the operating room and the drug has been administered, it will not be possible to exclude you from the study.

What will happen if you develop any study related injury?

We do not expect any study related injury to happen to you because both agents have been used for many years in anaesthetic practice, but if you do develop any side effects or problems it may be related to either the surgery or the anaesthetic drug. Any adverse events related to the anaesthetic drug will be treated at no additional cost to you.

Does Desflurane have any side effects?

Desflurane can cause restlessness during waking up especially in pediatric patients which could be due to early waking up and pain. Nausea and vomiting can happen occasionally as with any anaesthetic.

Will you have to pay for the study drug?

You will not have to pay any extra for the study drug. The cost of anaesthesia and the surgery will be the same as if you were not participating in the study.

After the study -

You may or may not benefit from this study, but the results of the study will provide important information about the possible advantage of using desflurane, in patients like you. These results may benefit other patients undergoing similar procedures in the future.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal and as part of a post-graduate thesis, but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by doctors and nurses associated with the study, without your additional permission, should you decide to participate in this study.

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: A prospective, randomized, double-blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of post-operative motor deficits in patients undergoing elective neurosurgery for supratentorial mass lesions.

Study Number: Hospital Number :

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter of/wife of _____

(Please tick boxes)
Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time before the surgery without affecting my usual treatment or my legal rights [ ]

I also understand that neither I, nor my doctors, will have any choice or knowledge of whether I will get desflurane or isoflurane during my surgery [ ]

I also understand that after the surgery, doctors will be frequently assessing me to look for any post-operative problems that I may have and they will assess the need for further investigations as required [ ]

I understand that I will receive treatment for any study related injury or adverse event but I will not receive any financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name of participant/relative/guardian: Name of witness:
Signature: Signature:

Date:

ATTENTION

PROTOCOL FOR THE DESFLURANE-ISOFLURANE RECOVERY STUDY

A prospective, randomized, double-blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of post-operative motor deficits in patients undergoing elective neurosurgery for supratentorial mass lesions.

INSTRUCTIONS FOR ANAESTHETISTS INVOLVED IN STUDY CASES

PRE-INDUCTION

1. Arrange for the MP50 monitor to be brought to the OR where the case is going to start – OR6/7/8.
2. Look at the patient data sheet/consent form for the study number of the patient.
3. Take the envelope corresponding to the study number, from the anaesthesia technician cupboard between OR 6 and 7. Each envelope will have the inhalational agent to be used written inside. Get the appropriate vapouriser.
4. Use only PROPOFOL (2mg/kg) for induction. Use vecuronium 0-15mcg/kg.
5. Use the time as seen on the MP50 monitor for all measurements.

INDUCTION

1. PROPOFOL for induction.
2. Total FENTANYL to be given at 3 mcg/kg
    a. 1 mcg/kg – at induction
    b. 1 mcg/kg – during scalp infiltration and pin placement
    c. 1 mcg/kg – during burr-hole making/drilling
    d. NO MORE FENTANYL TO BE GIVEN
3. VECURONIUM infusion to be started after induction- titrate dose to 2 twitches.
4. Note the TIME when starting all infusions.

MAINTENANCE

1. Keep the MAC for both desflurane and isoflurane at 0.8 only.

2. Ask the surgeon for Brain Relaxation Score (see data sheet) at opening of dura.
3. Give PERFALGAN for all cases after induction.

AT END OF THE CASE

Document the time when infusions are stopped :

Add 1 ampoule (75mg) of Diclofenac to the pint just before dural closure begins.

Stop VECURONIUM INFUSION when skin closure begins.

Stop INHALATIONAL AGENT without tapering once the head is removed from pins.Keep fgf of 100%O_2 at 8 l/mt.

Extubate when patient is still deep, and begin examining for recovery and deficits once extubated. Keep examining as given in data sheet till trolley arrives.

a. PLEASE COVER THE NAME OF THE AGENT USED ON THE YELLOW-SHEET (front and back) WITH THE BLACK TAPE PROVIDED. – for blinding purposes.
b. Please send ABG JUST AFTER EXTUBATION.

Abstract

Title: A prospective randomized double blinded study comparing the effects of Desflurane and Isoflurane on emergence from anaesthesia and recovery of postoperative deficits in patients undergoing elective neurosurgery for Supratentorial Intra Axial Mass Lesions.

Department: Departmant of Anaesthesia,Christian Medical College, Vellore

Degree and Subject: MD Anaesthesiology

Name of the giude: Dr.Grace Korula

Objectives: To compare the effects of desflurane and isoflurane anaesthesia in relation to -

1. Recovery as determined by the time to eye opening, time to extubation, time to obeying commands and orientation, after elective neurosurgery for adult patients (18-70 years, ASA I-III) with supratentorial intraxial mass lesions.

2. Time to improvement of early post-operative motor deficits within the first 12 hours after surgery.

Methods: The sample size initially chosen was 60 (18 – 70 years, ASA I-III) patients (30 patients in each arm) undergoing elective neurosurgery for supratentorial mass lesions. Inclusion Criteria for the study in elective neurosurgical patients with supratentorial intra-axial mass lesions was age 18 -75 years, ASA Grade 1-3, Pre-operative GCS – 15/15 and the exclusion criteria was previous craniotomy, Hepatic or renal disease,alcohol or drug abuse,hypothyroidism, BMI > 35 and any female patients who were pregnant/breastfeeding.This study was a double blinded trial. Clonidine was given as premedication.Induction was done with Propofol,total fentanyl given was 3 mcg/kg.Vecuronium 0.15 mg/kg was given at induction and infusion was started to maintain two twiches.MAC for both Desflurane and Isoflurane was maintained at 0.8. Brain Relaxation was assessed on opening the dura.Time to eye opening,time to extubation,time to obeying motor commands,time to orientation were calculated from the time of discontinuation of inhalational anaesthetic.A minineurological examination which assessed motor response and orientation was carried out after extubation and till 12 hours post-op. Data were entered into Epi Info 3.5.1 (CDC, Atlanta, GA), and analysed using SPSS 20.0 (Chicago, IL). Since the outcome variables were not normally distributed, time durations were presented as medians with 95% CI and the Mann-whitney U test was used to compare the two groups. Student t test was used to compare normally distributed variables.Statistical significance was set at $P < 0.05$.

Results:Our study showed that patients on desflurane had 35.7%,40% and 37.9%faster awakening with regard to time to eye opening, time to obeying motor commands and time to orientation.Neither Desfluarne or Isoflurane had significant effects on neurological deicits.

KEY WORDS:Randomised control study,desfluane,isoflurane,craniotomy for supratentorial lesions,awakenig,emergence and recovery of motor deficits